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DOI: https://doi.org/10.1016/j.prp.2008.12.011

Large Mixed Germ Cell Tumor in a young patient presenting as an intrapulmonary mass

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Running Title: Intrapulmonary Mixed Germ Cell Tumor

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Keywords: mixed germ cell tumor; mediastinal; extragonadal; clinical course; histology

Abstract

We present the case of a 26 year-old man with a bland medical history who presented to the general practitioner due to severe cough and dyspnea. The chest x-ray revealed a massive organ displacing tumor in the right chest not delineable from the mediastinum. The subsequent needle core biopsy was diagnostic for a mixed germ cell tumor comprising immature teratoma and seminoma. After an initial good response to chemotherapy, tumor markers and tumor size were progressive. The right-sided pneumonectomy revealed an intrapulmonary tumor with cystic and solid components, hemorrhage and necrosis with a tumor diameter of eighteen cm. Histology confirmed a teratoma with mature and immature components accompanied by residual seminomatous tumor cells. Despite maximal intensive care the patient died four weeks after surgery from an acute respiratory distress syndrome. We thoroughly describe this exceptional large intrapulmonary germ cell tumor and discuss the spectrum of such rare tumors.

Introduction

Frequent tumors detected as mediastinal masses by modern imaging techniques include thymomas, lymphomas, thyroid carcinomas, esophageal carcinomas and germ cell tumors[34, 36]. The latter ones are either metastases from testicular or ovarian tumors or aroused de novo at this location (hypothesized from primitive germ cells). Up to ten percent of germ cell tumors are extragonadal with the mediastinum being the most common extragonadal site in adults, harbouring around 3-4% of these tumors [19, 32]. Germ cell tumors account for up to 20% of all mediastinal tumors with seminomas and teratomas being the most frequent. About 27% of all teratomas occur in the (mainly anterior) mediastinum. Teratomas are composed of two or more of the three embryonic germinal layers: ecto- endo- and mesoderm. According to their degree of differentiation teratomas are designated as mature – consisting of fully differentiated tissue components – or immature – displaying purely or partially immature/undifferentiated i.e. embryonic-like tissue components. Whereas the mature teratomas have a generally benign course and are cured by surgical resection, the immature teratomas are potentially malignant and have the ability to metastasize. Unfortunately a clinical (e.g. radiological) distinction between these two clinically important types is impossible. Since macroscopically mainly mature teratoma can harbour immature components the definite diagnosis is made by histological analysis of a thoroughly sampled specimen. The immature tissue components display most often neuroectodermal or mesenchymal (spindled stroma) features[19]. The former should be distinguished from mature ependyma (almost no mitotic figures) and from the mature teratoma[19]. The amount of immature tissue in relation to remaining differentiated tissues is the basis for a grading of teratomas. However, the prognostic value of such a grading is not confirmed and not recommended for extragonadal teratomas and mixed germ cell tumors but the extent

of immature tissue is proposed to be reported in the diagnosis[19, 32]. The average size of mediastinal tumors, including mature teratomas and mixed germ cell tumors is about 10 cm, but large cases (21 to 28 cm) have also been described[22, 32]. The weight of these tumors ranges between 48g and 2000g. Immature teratomas might be as large as 40 cm[32]. Malagon *et al*. analyzed mixed GCT with a sarcomatoid component and found 4 of the 23 primary mediastinal mixed GCT with immature teratomatous components (all stage III). Three of these patients died (2/3) during follow-up or experienced progressive disease(1/3)[17].

Materials and Methods

Radiologic images (x-ray, computed tomography, positron emission tomography). Surgical dissection was performed according to in-house standard protocols with thorough tissue sampling of tumor tissue. Hematoxyline & eosin stains with histological and immunohistological work-up (hematoxyline & eosin, CD117, CD30, PLAP, beta HCG, AFP) were all performed according to standard protocols.

Results – case report

Six month ago, a 26 year old patient of Italian descent presented to the general practitioner with massive cough and dyspnea. The patient quitted smoking half a year ago and had a smoking history of one pack year. There was no history of any relevant medical problems.

A subsequently performed chest x-ray displayed a large tumor in the right hemithorax not delineable from the mediastinum (Figure 1A). A biopsy taken from the tumor revealed a malignant germ cell tumor consisting of seminomatous and immature teratomatous components. The Alpha fetoprotein (AFP) and human choriongonadotropin beta (beta-HCG) were elevated at 5139 µg/l and 14.8 IU/l

respectively. A chemotherapeutic approach was decided on and the patient received five cycles of chemotherapy with efosfamid, etoposid and cisplatin which resulted in a reduction of AFP levels to 33.6 µg/l. For the sixth and last cycle he received bleomycin. Under bleomycin the patient complaint about dyspnea, fatigue and peripheral paraesthesia. A subsequent follow-up computed tomography (Figure 1B) showed a slight progression in tumor size but a reduced tumor perfusion. In the positron emission computed tomography the tumor was fluorodeoxyglucose negative without circumscribable borders to the mediastinal pleura, pericard and diaphragm. Nevertheless the tumor was regarded resectable. The pre-operative examinations showed an AFP level of 2.7 µg/l, dyspnea after one flight of stairs, missing breath sounds on the right side and tachycardia (130 bpm) at rest. The tumor was surgically resected by performing a right-sided pneumectomy.

The surgical specimen measured 21x20x16 cm and weighted 3000 g. The lobes of the right lung were massively dislocated and compressed. The inferior lobe was almost completely absorbed by an encapsulated 18x16x12 cm solid/multi-nodular and partially cystic and necrotic tumor (Figure 1C). There were no signs of pleural involvement. The other two pulmonary lobes were without signs of tumor invasion too. Histologically, the tumor consisted of a mixture of immature (about 30 %) and mature components of the three germ cell layers (respiratory, intestinal, neuronal, osseous and chrondroid tissue (Figure 1D)), being diagnostic for an immature teratoma. Immunhistologically, small areas of CD117 positive dyscohesive tumor cells (Figure 1 E) could be demonstrated, representing remnants of the seminomatous compartment of the tumor. Additionally we could identify small areas with AFP positive tumor cells (Figure 1F). On several sides of the tumor residual pulmonary tissue was detected and the tumor seemed rather displacing than infiltrative in these parts. Inside the tumor no genuine pulmonary parenchyma was

found. The sparse attached mediastinal tissue was completely embedded and consisted of fatty tissue and thymus tissue remnants but did not present any tumor residues. The diagnosis of a mixed germ cell tumor was confirmed and the immature component of the teratomatous part was stated with about 30%. A comparison with the biopsy specimen (Figure 1G-I) revealed a stronger staining for CD117 and positivity for PLAP (Figure 1G) as well as the typical dot-like cytokeratin staining of the seminomatous component (Figure 1H). The teratomatous part was also present in the biopsy (Figure 1I). A tumor of the testes was not known nor was there any clinical evidence of it. Due to the encapsulated growths and size of the tumor it was not possible to definitely decide whether the tumor was of intrapulmonary or mediastinal origin.

In the post-operative course, the patient developed respiratory insufficiency caused by acute respiratory distress syndrome or possible bleomycin induced damage with complete respiratory failure warranting extracorporale membrane oxygenation and intensive medical care. The patient developed fever of unknown cause. Postoperative computed tomography revealed hypodense intrahepatic lesions considered to be metastases (Figure 1J). The patient died four weeks after surgery. An autopsy was not performed for the family of the patient did not consent to it.

Discussion

The presented case demonstrates the radiological and pathological findings associated with these rare tumors in young patients. The most important prognostic parameters of mediastinal germ cell tumors are tumor stage and completeness of surgical resection[30]. Complete excision is sometimes difficult due to large tumors and adhesions with neighboring organs and pneumonectomy might be unavoidable[35]. However, the survival rates for patients with residual tumor are below 10%. Therefore

surgical resection following a cisplatin-based therapy remains to be the current standard therapy[2, 32, 35]. If responsive to chemotherapy the 5 year survival times in a recent study where above 80%[16]. Chemotherapies with bleomycin were more often associated with post-operative respiratory complications and death[14].

Other prognostic factors for non-seminomatous and mixed germ cell tumors are patient age, anatomic site of the tumor, existence of metastasis, elevated beta-hCG levels and the amount of immature tumor tissue[4, 5, 18, 32]. The post-chemotherapy histology is another prognosticator with stepwise lower survival rates for patients with residual viable tumor, viable teratoma, viable non-teratomatous GCT components or viable malignant somatic tumor[8, 9, 28].

The number of published mediastinal or intrapulmonary mixed GCT with their various subtypes is small. Most publications with reported survival times contain less than 30 of such cases and/or divide the tumors only into non-seminomatous or mixed GCT without further stratification according to the different histologic components. Therefore the reliability of survival data for such cases is limited.

In our case we could not completely exclude a mediastinal origin because it is possible that mediastinal parts of the tumor might have been destroyed by the chemotherapy. However, the clinical findings and radiological images were highly suggestive of an intrapulmonary GCT, although the mediastinal pleura was not delineable on cross-section images due to the size of the tumor. A testicular origin seemed unlikely since all clinical investigations during the whole course of the disease remained unsuspective. However, since the patient's relatives refused an autopsy this could not definitely be ruled out. Primary intrapulmonary germ cell tumors are quite rare with only few chorioncarcinomas, yolk sac tumors, embryonic carcinomas and very few mixed GCT reported[10, 13, 20, 24-26, 33]. Most mixed germ cell tumors were macroscopically poorly circumscribed with an invasive growth pattern[32].

In our case the tumor was well circumscribed without frank infiltration of adjacent tissue. Intrapulmonary teratomas are very rare and like mediastinal ones thought to be derived from ectopic thymic tissue (third pharyngeal pouch)[3, 7, 12, 27]. Most of them occur in the first two to four decades of life and predominantly in the upper lobe and on the left side[11, 23, 29, 31, 32, 37]. For intrapulmonary teratomas a slight female preponderance is proposed[32] whereas for mediastinal germ cell tumors other than teratomas a clear predilection of men has been demonstrated [22].

The majority (about two third) of intrapulmonary teratomas is benign (mature) and complete surgical resection was the therapy of choice for immature and mature tumors. Since many immature teratomas were unresectable most patients died after a short period of time[23, 32]. Computed tomography can detect fat, calcifications (e.g. bone, teeth), soft tissue, cysts and fluids as typical components of teratomas (mature)[21]. In cases where the size of the tumor hinders an exact localization peripheral translucency (computed tomography) and direct communication with the bronchi are considered as differentiating between intrapulmonary and mediastinal teratomas[23, 37]. Typical clinical and anamnestic symptoms of intrapulmonary as well as mediastinal tumors are cough (sometimes expectorative), dysnea, fever and chest pain[15, 23, 27].

Mixed germ cell tumors, mainly teratomas with additional malignant components (e.g. other germ cell tumors, carcinomas or sarcomas), were described as more aggressive. More than 50% of those patients died within 2 years of follow-up due to local invasion or distant metastases (lymph nodes, liver, lung, heart, bone and brain)[22, 32]. The progression of tumor size in combination with reduced AFP levels as seen in our case could either be due to the chemotherapy resistance of non-AFP-secreting tumor components or part of the so-called growing teratoma syndrome (increase in size and normalization of serum markers during or after chemotherapy

with histological findings of exclusively mature teratoma)[1, 32] with the chemotherapy inducing further differentiation of the formerly immature tumor components. The nomenclature of mixed germ cell tumors is not consistent. Moran *et al.* proposed the term “teratoma with malignant component” which should be further subdivided according to the histologic type of that component. Such a classification goes beyond the current scheme of the World Health Organization (WHO) which subsumes all these tumors under the mixed germ cell category[6, 22, 32].

Moran *et al.* proposed a three-step clinical staging dividing well-circumscribed tumors (I) from those with marco/microscopical invasion into adjacent structures (II) and those with thoracic or extra-thoracic metastasis (III), suggesting aggressive curative treatment options for the first two and palliative treatment for stage III tumors[6, 22].

Whether the use of these categorizations can be further validated and whether they will be included in the new WHO classifications remains to be seen.

Acknowledgements

We thank Norbert Wey for excellent technical and Prof. J. Diebold for logistic support.

Figure legend

Figure 1 Radiological and pathological findings of the presented case

A Chest x-ray of the patient displaying a large organ displacing mass on the right chest not delineable from the mediastinum and pleural effusion. **B** Axial computed tomography image confirms the results from the x-ray showing a large heterogeneous mass with calcifications compressing the right lung. The lesion displaces the mediastinal structures to the left. Due to the size a precise allocation to either the mediastinum or lung is not possible. **C** Macroscopic specimen demonstrating the massive tumor with cystic, solid and hemorrhagic areas and

residual lung parenchyma on the right side. **D** Histologic specimen (magnification 200x) of the tumor containing respiratory, immature, chondroid and fibrous tissue components. **E1/2** Immature parts of the resected tumor with seminomatous component (CD117 positive). **F** Focal alpha fetoprotein positive tumor component. **G1-3** Seminomatous tumor component in the biopsy specimen with positivity for PLAP (**G2**) and CD117 (**G3**). **H1/2** Seminomatous biopsy specimen with typical dot-like expression of pan-cytokeratin (**H2**). **I1/2** Teratomatous component in the biopsy specimen with focal cytokeratin positivity. **J** Postoperative computed tomogram with three hypodense intrahepatic tumors suspect for metastases.

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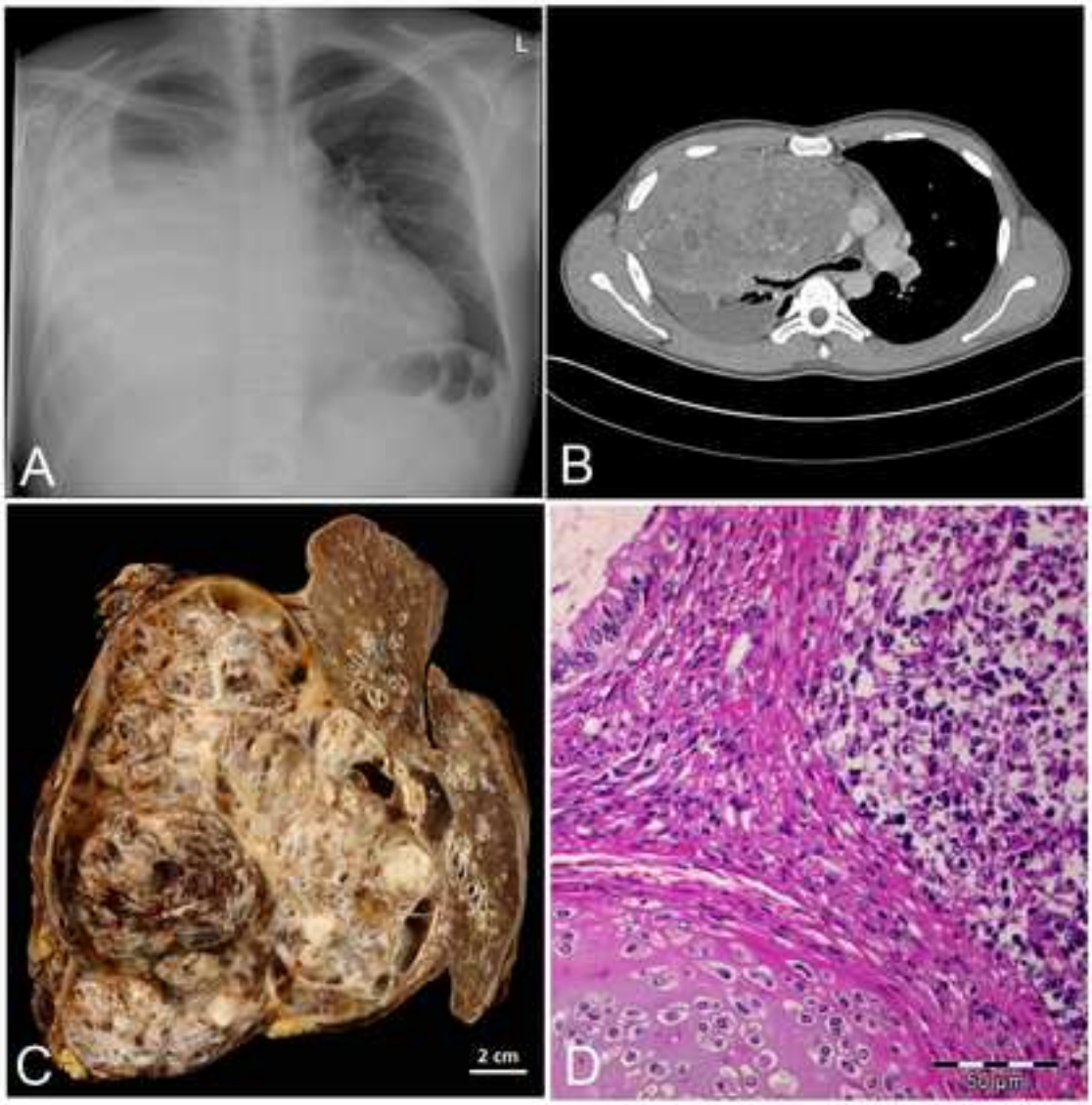
Fritzsche/Montani et al. Figure 1 A-D



Fritzsche/Montani et al. Figure 1 E-J